REMARKS

Claims 24 – 28 and 32 – 35 are currently pending. Claim 24 has been amended. Applicants request reconsideration and allowance of all pending claims.

Amendments to the Claims

Claim 24 has been amended to provide proper antecedent basis and correct a typographical error.

Rejection of the Claims under 35 U.S.C. § 103(a)

Reconsideration is requested of the rejection of claims 24 – 28 and 32 – 35 under 35 U.S.C. §103(a) as being unpatentable over Cook (U.S. Pat. No. 6,213,930) in view of Dráber et al. ("Stability of monoclonal IgM antibodies freeze-dried in the presence of trehalose," J. Immunol. Meth., Vol. 181, p. 37-43 (1995)); Andya et al. ("The effect of formulation excipients on protein stability and aerosol performance of spray-dried powders of a recombinant humanized anti-IgE monoclonal antibody," Pharm. Res., Vol. 16, p. 350-358 (1999)); and Freeman (U.S. Pat. No. 6,746, 698).

Claim 24, as amended herein, is directed to a method for producing a feed containing heat-stabilized egg antibodies. The method comprises the steps of: mixing an egg white, an egg yolk and at least one saccharide selected from a monosaccharide, a disaccharide, a polysaccharide, an alkylated monosaccharide, an alkylated disaccharide, an alkylated polysaccharide, a monosaccharide alcohol, or an alkylated monosaccharide alcohol to form an egg liquid suspension, said egg yolk containing an egg antibody produced in response to antigen inoculation; and spray drying the egg liquid suspension to form an egg powder; and processing

the egg powder to provide a feed containing heat-stabilized egg antibodies, said processing step including exposing the egg powder to an antigen-binding-activity-destroying temperature of at least 70°C; wherein the heat-stabilized egg antibodies in the feed produced by said method loses less of its antigen-binding activity in comparison to an egg yolk antibody retaining at least 20% of its antigen-binding activity after being exposed to said antigen-binding-activity-destroying temperature.

Cook discloses a method for enhancing growth or feeding behavior of an animal by administering an agent that reduces the bioavailability of a prostaglandin or leukotriene lipid precursor, wherein the agent is an antibody. Cook further discloses that the antibody can be an anti-phospholipase A2 antibody prepared by inoculating a chicken hen to produce a preparation of egg-yolk antibodies. *See*, Cook at column 4 lines 4-13. An egg preparation containing the antibody is then prepared and administered to the desired animal. *See*, Cook at column 4 lines 14-22. Significantly, Cook fails to disclose or suggest a method for producing a feed containing heat-stabilized egg antibodies. Moreover, as the Office recognizes Cook does not teach the use of a saccharide (e.g., trehalose) and does not teach a processing step at a temperature of at least 70°C. And, as Cook fails to disclose or suggest these limitations, the Office attempts to combine the Cook reference with Dráber et al., Andya et al., and Freeman to arrive at each and every limitation of Applicants' claimed invention.

Dráber et al. disclose a method for freeze-drying and long-term storage of monoclonal IgM antibodies using trehalose. *See*, Dráber et al. at page 37, abstract.

Andya et al. disclose the effect of formulations using excipients on protein stability and aerosol performance of spray-dried powders of a recombinant humanized anti-IgE monoclonal antibody. *See*, Andya et al. at page 350.

The Office cites Freeman for disclosing a general method for producing animal feed. Significantly, the cited references, alone or in combination, fail to disclose or suggest a method for producing a feed containing heat-stabilized egg antibodies wherein the method includes a processing step of exposing the mixture to a temperature of at least 70°C.

In the instant case, the Office stated that it would have been obvious to one of skill in the art to use trehalose with anti-PLA_2 antibody because trehalose confers thermostability to dried formulations. The Office also stated that it would have been obvious to form pellets for feeding different size animals using conventional methods taught in Freeman. The Office further stated that during pelleting, trehalose would confer thermostability to the animal feed mixture taught by Cook. *See*, Office Action at page 4 first full paragraph. The Office, however, failed to cite any of the references to support this conclusory statement. Specifically, the Office simply states the secondary reference[s] (i.e., Dráber et al., Andya et al., and Freeman) provide motivation to use saccharide and motivation to form tablets or pellets for animal feed, thereby exposing the feed to temperatures greater than 70°C. At best, the Office asserts that the motivation for the use of trehalose is that it confers thermostability to dried formulations (citing Dráber et al. and Andya et al.).

For the Office to show a *prima facie* case of obviousness, M.P.E.P. § 2142 requires a clear articulation of the reasons why the claimed invention would have been obvious. Specifically, the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82

USPQ2d 1385, 1396 (2007) noted that the burden lies initially with the Office to provide an explicit analysis supporting a rejection under 35 U.S.C. § 103. "[R]ejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." The Court in *KSR International* further identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as set forth in *Graham v. John Deere Co.* (383 U.S. 1, 148 USPQ 459 (1966)).

Specifically, as previously required by the TSM (teaching, suggestion, motivation) approach to obviousness, one exemplary rationale indicated requires some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. To reject a claim based on this rationale, the Office must articulate the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at each and every limitation of the claimed invention; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. The Office has failed to meet its burden under number (1) above, as there is no apparent reason for one skilled in the art to modify or combine the references to arrive at each and every limitation of Applicants' claims.

Applicant respectfully disagrees with the Office that one skilled in the art would combine the references in a manner to arrive at the claimed invention. In determining obviousness, 35 U.S.C. § 103(a) expressly requires considering the claimed invention <u>*as a whole*</u>. According to

the Federal Circuit, "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965); see also, *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448-49 (Fed. Cir. 1986) (holding that the district court, by failing to consider a prior art reference in its entirety, ignored portions of the reference that led away from obviousness). Furthermore, "[t]he 'as a whole' instruction prevents evaluation of the invention part by part. . . This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result – often the very definition of invention." *Ruiz v. A.B. Chance co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004). Moreover, "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." *See*, MPEP § 2143.03 (citing *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)).

In the instant case, the Office argues that the primary reference, Cook, teaches the preparation and use of anti-phospholipase A_2 antibodies to enhance growth or improve animal feed. When considered as a whole, Cook discloses a method for enhancing growth, feeding behavior, and *improving feeding efficiency* by administering an agent (e.g., anti-PLA2 antibody in an egg powder) to reduce gastrointestinal inflammation. *See*, Cook, abstract, column 2 lines 59-65, column 4 lines 14-22, and claim 1. Cook does not teach producing an animal feed containing heat-stabilized egg antibodies wherein the egg antibodies are subjected to a processing step including heating at temperatures of at least 70°C as required in the instant application. In fact, Cook merely describes the same type of antibody against PLA_2, no where

does Cook suggest that the antibody may be heat-stabilized according to the methods of the claimed invention. *See*, Specification at page 6 Example 1, paragraph [00025] – page 7, paragraph [00028].

Combining Cook with Dráber et al., Andya et al., and Freeman does not render obvious claims 24 – 28 and 32 – 35 of the instant invention. Considered as a whole, both Dráber et al. and Andya et al. teach methods of stabilizing antibody preparations during drying for the purpose of long-term storage at temperatures up to 50°C. Freeman is merely cited by the Office for providing conventional methods for feed pelleting. Significantly, none of the references cited by the Office can be fairly read or interpreted as teaching or suggesting protecting antibodies from *the destructive effect of heat* as in the instant invention (*see*, Specification at page 3, paragraph [00011]).

As noted above, Dráber et al., in fact, solves an entirely different problem than the instantly claimed invention. Dráber et al. teaches a *cryopreservation* method whereby a monoclonal antibody is freeze-dried in the presence of trehalose to avoid irreversible denaturing that occurs by freeze-drying. *See*, Dráber et al. at page 37, right column (citing Groding, 1986). Thus, the method taught in Dráber et al. takes advantage of the known *cryopreservative* properties of trehalose to protect antibodies from *the destructive effect of freezing temperatures*, whereas the instant invention claims a method for protecting antibodies from *the destructive effect of heat* (*see*, Specification at page 3, paragraph [00011]). Thus, one skilled in the art would not have reason to combine the cryopreservation methods taught in Dráber et al. with Cook and/or Andya and/or Freeman when seeking methods to protect antibodies from the destructive effect of heat as claimed in the instant application. Therefore, Applicants submit that combining Dráber et al. with Cook and/or Andya and/or Freeman constitutes an impermissible

picking and choosing from the teaching of Dráber et al. to support the Office's position to the exclusion of other parts necessary for the full appreciation of what Dráber et al. fairly suggests to one of ordinary skill in the art, which is improper under the § 103 obviousness analysis.

As in Dráber et al., Andya et al. teach methods of stabilizing antibody preparations during drying for the purpose of long-term storage at temperatures up to 50°C, not protecting antibodies from *the destructive effect of heat* as in the instant invention. Although Andya et al. describe using trehalose with the spray drying process, when read as a whole, the Andya et al. teaching is to address the problem of stabilization of antibody preparations during drying for the purpose of long-term storage. *See*, Andya et al. at page 350, abstract and right column, first full paragraph. Thus, as with Dráber et al., one skilled in the art would not have reason to combine the method of using trehalose for stabilization of antibody preparations during drying for the purpose of long-term storage taught in Andya et al. when seeking to protect antibody preparation from *the destructive effect of heat* during feed production as in the instant invention.

At pages 5-6 of the instant final Office action, the Office states that "[i]t is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." While Applicants agree that the art need not suggest the same advantage, the art must suggest a reason for modifying/combining their methods to arrive at the instantly claimed method of exposing the egg powder to an antigen-binding-activity-destroying temperature of at least 70°C. There is simply no reason to do so. As noted above, while Dráber et al. and/or Andya et al. teach or suggest the protein stabilizing effect for storage at temperatures up to 50°C, there is nothing to suggest the use of a saccharide to provide protection of the antibodies during *the destructive effect of exposure to heat* at temperatures of at least 70°C, as required in

Applicants' claimed invention. One skilled in the art, reading the cited references, would simply not make such a modification.

Based on the teachings of Dráber et al. and Andya et al. that trehalose provides an antibody stabilizing effect at temperatures up to 50°C, one skilled in the art would not combine these references with the conventional feed pelleting or tablet formation methods disclosed in Freeman, which disclose temperature of up to 120°C, to arrive at the claimed invention. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." MPEP § 2143.01 (citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1396 (2007)). The specification of the instant invention points out that it is well known that IgG is denatured at a temperature of 70°C. *See*, Specification at page 2, paragraph [0004] (citing Hajime Hatta et al., Biosci. Biotech. Biochem. 57:450-454, 1993). Moreover, Dráber et al. teach that IgM is less robust than IgG (see, Dráber et al. at page 37, right column). Thus, one skilled in the art would not expect IgM to remain undenatured at temperatures (i.e., greater than 70°C) that result in the denaturation of IgG. Other studies show IgE is heat-inactivated at temperatures of 56°C. See, Demeulemester et al., "Thermoinactivation of human IgE: antigenic and functional modifications," Immunology Vol. 4: 617-20 (1986). Nothing in Dráber et al., Andya et al. and/or Freeman teach or suggest that the protein stabilizing effect for storage at temperatures up to 50°C could predictably provide protection of antibodies during exposure of heating at temperatures of at least 70°C as required by the instant application or at even higher temperatures disclosed in Freeman. Therefore, because one skilled in the art could not predict from Dráber et al. and/or Andya et al. that methods for storing antibody preparations at up to 50°C could protect antibodies from *the destructive effect of heat at antigen-binding-activity-destroying temperatures*

of at least 70°C according to the claimed invention, it would not be obvious to one skilled in the art to further combine the references with conventional methods for preparing feed pelleting and tablet formation disclosed in Freeman.

With respect to claims 25-28, Dráber et al. and Andya et al. teach away from using any sugar other than trehalose. For example, Dráber et al. state,

> "Of the other sugars tested, only the non-reducing disaccharide sucrose (β-D-fructofuranosyl-α-D-glucopyranoside) that is often used as a cheap protectant during the freeze-drying of proteins provided some protection for freeze-dried IgM mAb stored at high temperatures. However, its protective efficiency did not reach that of trehalose. Sucrose is stable as a pure substance but in the presence of chemically reactive amino groups of proteins it splits into the reducing monosaccharides glucose and fructose. The prolonged storage of susceptible dried proteins in reactive sugars can *thus lead to chemical damage in the proteins*." (emphasis added).

See, Dráber et al. at page 41 right column, final paragraph continuing to page 42, left column. Like Dráber et al., Andya et al. conclude that lactose resulted in chemical protein modification (i.e., glycation) during storage and mannitol was susceptible to crystallization. *See*, Andya et al. at page 357, right column under the heading, "Conclusions". Thus, both Dráber et al. and Andya et al. would lead one skilled in the art away from using a monosaccharide, a disaccharide, a polysaccharide, an alkylated monosaccharide, an alkylated disaccharide, an alkylated polysaccharide, a monosaccharide alcohol, or an alkylated monosaccharide alcohol other than trehalose for producing a feed containing heat-stabilized egg antibodies because of the potential for chemical damage, modification or stability in the proteins. Therefore, claims 25-28 are non-obvious over Cook in view of Dráber et al. and/or Andya et al.

Because one skilled in the art would not look to methods for stabilizing antibody preparations such as anti-PLA_2 as disclosed by Cook for the purpose of stabilization during

drying and long-term storage at temperatures up to 50°C as disclosed by Dráber et al. and/or Andya et al., one skilled in the art would not have reason to combine these references with Freeman. As recognized by the Office, Freeman discloses conventional methods to form tablets or pellets for animal feed, thereby exposing the feed to temperatures greater than 70°C. The Office asserts that the motivation for the use of trehalose is that it confers thermostability to dried formulations as disclosed by Dráber et al. and/or Andya et al. Nothing in the references fairly teaches or suggests that thermostability conferred to dried antibody formulations by trehalose at temperatures of up to 50°C as disclosed by Dráber et al. and/or Andya et al. would be predicted to confer thermostability against when exposing the antibody to *temperatures of at least 70°C* as claimed in the instant application. Therefore, the claims of the instant application are non-obvious over Cook in view of Dráber et al., Andya et al., and/or Freeman.

Based on the foregoing, it simply would not have been obvious to one skilled in the art to combine Cook with Dráber et al., Andya et al., and Freeman to arrive at Applicant's claimed invention. Further, considering the references as a whole clearly establishes that combining the references in the manner suggested by the Office involves hindsight reasoning using the instant invention as a roadmap. Therefore, because there is no reason in the prior art that would have led one of ordinary skill to modify or combine the prior art references to arrive at the claimed invention, Applicant respectfully requests allowance of claims 24-28 and 32-35 of the instant application.

CONCLUSION

In view of the above, Applicants respectfully request favorable reconsideration and allowance of all pending claims. The Commissioner is hereby authorized to charge any fee deficiency in connection with this Amendment and Response After RCE to Deposit Account Number 01-2384.

Respectfully submitted,

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